

Desensitization Protocols for Vancomycin Hypersensitivity

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OBJECTIVE: To discuss the pathophysiology of vancomycin-induced immediate hypersensitivity reactions, review the process of vancomycin desensitization, and provide specific directions for ordering and preparing rapid and slow desensitization protocols.

DATA SOURCES: A MEDLINE search (1966–February 2001) of English-language literature pertaining to vancomycin desensitization and hypersensitivity reactions was performed. Tertiary sources were also used.

DATA EXTRACTION: Published clinical studies and case reports.

DATA SYNTHESIS: The pathophysiology of vancomycin-induced hypersensitivity reactions is discussed along with the procedure of vancomycin desensitization. Desensitization should be considered in Red Man syndrome (RMS) that does not respond to the usual treatment measures, and in vancomycin-induced anaphylaxis. Rapid desensitization is preferred as it is effective in the majority of patients and enables therapeutic dosing of vancomycin within 24 hours. In patients who fail rapid desensitization, a slow desensitization protocol may be tried.

CONCLUSIONS: Vancomycin-induced immediate hypersensitivity reactions include RMS and anaphylaxis. Vancomycin desensitization should be considered for severe RMS reactions not responding to usual measures and in anaphylactic reactions to vancomycin, when substitution of another antibiotic is not feasible.

KEY WORDS: anaphylaxis, Red Man syndrome, vancomycin.

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Hypersensitivity reactions to vancomycin include Red Man syndrome (RMS) and anaphylaxis. By far the most common hypersensitivity reaction is RMS, with studies reporting an incidence of 3.7%¹ to 47%² in infected patients and up to 90%³ in healthy volunteers. Anaphylactic reactions, on the other hand, are rare but do occur. The exact incidence of anaphylaxis is not known.⁴ Although newer antibiotics have become available for the treatment of β -lactam-resistant gram-positive infections, vancomycin remains the agent of choice.⁵ As the rates of these resistant infections continue to grow,⁵ the clinician can expect to encounter more patients with vancomycin-induced hypersensitivity reactions. For patients with these resistant infections who experience severe RMS or who present with anaphylaxis, vancomycin desensitization is a reasonable

option and can be performed successfully in the majority of cases.

Vancomycin-Induced Hypersensitivity Reactions

Hypersensitivity reactions to vancomycin occur via two different mechanisms. While both reactions involve mast-cell activation, vancomycin-induced anaphylactic reactions are mediated by immunoglobulin (Ig) E, while anaphylactoid reactions (i.e., RMS) are not. Although the reactions occur through different mechanisms, in some patients the clinical presentation may be identical.^{6,7}

RMS, the characteristic anaphylactoid reaction to vancomycin, is dose dependent and associated with rapid infusions of large doses.⁸ RMS has been reported³ in 80–90% of healthy volunteers administered 1 g of vancomycin over one hour. Patients being treated for infections, however, may have a lower reaction rate and less severe RMS than

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healthy volunteers or patients receiving vancomycin for preoperative prophylaxis.⁹ The presence of bacteria, malignancy, and diabetes have all been shown to alter response to and release of histamine.⁹ Two studies that examined hospitalized patients receiving treatment with vancomycin 1 g over one hour reported RMS incidences of 3.4%¹ and 47%.²

RMS occurs due to histamine release from mast cells and basophils located in the skin, lung, gastrointestinal tract, myocardium, and vascular system.^{3,8} The reaction usually occurs with the first dose, but may occur at any time.¹⁰ Patients typically present with generalized flushing, pruritus, and an erythematous rash; hypotension, chest pain, and dyspnea have been reported in more severe reactions.¹¹ Hypotension without the appearance of a rash has also been reported.^{12,13} The severity of the reaction is proportional to the amount of histamine released.¹⁰

Strategies to prevent the occurrence of RMS have been proposed. One strategy is to slow the infusion rate of vancomycin since there is a direct correlation between the infusion rate and development of RMS. In one study,¹⁴ in which patients were given vancomycin prophylaxis for elective arthroplasty, 100% of subjects who received a rapid infusion of vancomycin (1 g over 10 min) developed a rash. A comparison of the effect of one- and two-hour infusions of vancomycin 1 g in 10 healthy adult male volunteers was performed.⁹ Eight subjects had evidence of RMS during the one-hour infusion while only three had signs or symptoms during the two-hour infusion ($p < 0.05$). Another option is to administer smaller doses more frequently. When 11 healthy volunteers were administered three doses of vancomycin 1 g every 12 hours, nine subjects experienced RMS. When administered five doses of 500 mg every six hours, none had a reaction.³

Prophylaxis using a histamine, H₁ receptor antagonist should also be used to decrease histamine release.^{8,9,15} Intravenous diphenhydramine 1 mg/kg, oral hydroxyzine 50 mg, and oral diphenhydramine 50 mg have been demonstrated to be effective in the prevention of RMS.^{2,14,15} Oral antihistamines are as effective as the intravenous formulation in ameliorating the reaction, but should be given at least 45–60 minutes before vancomycin infusion.^{2,14,16} Interestingly, combining H₁ and H₂ receptor antagonists in the treatment of vancomycin-induced RMS does not appear to provide any significant benefit in ameliorating symptoms compared with use of H₁-receptor antagonists alone.¹⁵ Although tolerance to RMS may rapidly develop,¹⁰ it is recommended to employ the aforementioned preventive measures to alleviate the patient's discomfort with subsequent doses. Thus, when RMS is observed, the first step is to administer antihistamine prophylaxis and either increase the infusion time to two hours or administer smaller doses every six hours.^{3,9} RMS that develops despite using these measures likely represents a severe variant of the syndrome in which the mast cells and/or basophils are much more readily degranulated by vancomycin.¹⁷ This patient subgroup will require desensitization if administration of vancomycin is to be continued.^{17,18}

The second type of immediate vancomycin-induced hypersensitivity reaction is IgE-mediated systemic anaphylaxis. In order for anaphylaxis to occur, the patient must first become sensitized to vancomycin with production of vancomycin-specific IgE.⁶ Repeat vancomycin administration results in cross-linking of IgE receptors on the sensitized mast cells, causing them to release vasoactive mediators such as histamine, leukotriene C₄, and prostaglandin D₂.⁷ Cytokines such as tumor necrosis factor alpha (TNF- α), and interleukins 4, 5, 6, 8, and 13 may amplify the reaction.⁷ The early phase of IgE-mediated reactions involves local edema, smooth muscle contraction, vasodilatation, and increased permeability of postcapillary venules, whereas the late phase involves the recruitment and activation of basophils, eosinophils, and other cell types, and may persist for 48 hours.¹⁹ The inflammatory cascade is life threatening unless medical treatment is immediately obtained.

Epinephrine is the first-line agent used in the treatment of anaphylaxis. Epinephrine inhibits histamine release and antagonizes the histamine-induced vasodilation and capillary permeability, thereby preventing circulatory collapse. No studies have examined whether there is a role for premedication with epinephrine during desensitization to prevent anaphylaxis. However, 0.3 mL of epinephrine 1:1000 strength has been administered subcutaneously during a desensitization procedure to alleviate mild hypotension and oxygen desaturation, allowing the desensitization to continue.²⁰ Antihistamines are not useful in the acute anaphylactic reaction as they do not reverse the effects of histamine.²¹ However, they may be initiated to prevent the development of late reactions such as urticaria, hypotension, or recurrent bronchospasm.^{21,22} Corticosteroids are also not effective during an acute anaphylaxis, but may alleviate occurrence of late reactions.²² For these reasons, both antihistamines and corticosteroids have been used as premedications in desensitization procedures.

Although anaphylactic reactions to vancomycin are mechanistically different from severe RMS, in some cases the two may be clinically indistinguishable. In either instance, vancomycin desensitization is recommended due to the severity of the hypersensitivity reaction.

Skin Testing, Histamine and Tryptase Assays

Presently, there are no methods available to identify patients at risk for vancomycin-induced hypersensitivity reactions. Skin testing with vancomycin is likely to produce false-positive results because it directly degranulates mast cells on intracutaneous administration.²³ Assays are available to measure histamine release as a marker of mast-cell activation; however, they are generally used only in the research setting due to the onset and elimination profile of histamine. Histamine concentrations peak five minutes following the onset of an immediate hypersensitivity reaction and decline rapidly, with a half-life of only a few minutes.²⁴ Plasma histamine concentrations usually return to baseline within one hour following an immediate hypersensitivity reaction, thereby limiting their clinical utility.²⁵

More recent investigations have examined the use of tryptase concentrations as a clinical indicator of mast-cell activation.^{26,27} Tryptase is a protease enzyme found in secretory granules of human mast cells. Mast-cell degranulation results in release of tryptase into the systemic circulation. β -Tryptase selectively concentrates in the secretory granules of human mast cells²⁸; α -protryptase is the predominant type of tryptase in normal human serum.²⁹ Total tryptase concentrations include both isoforms. Generally, total tryptase concentrations increase more than 100%³⁰ and the ratio of peak total tryptase to peak β -tryptase is >10 during immediate hypersensitivity reactions.²⁹

One study¹⁶ suggests that tryptase concentrations are not increased during vancomycin-induced anaphylactoid reactions; this would allow tryptase to be used to distinguish vancomycin-induced anaphylactoid from anaphylactic reactions. Unfortunately, only total tryptase concentrations were measured in this trial and the blood samples were collected 10 minutes after a rapid vancomycin infusion. A major criticism of this study's findings is that peak concentrations of tryptase occur one to two hours after immediate hypersensitivity reactions and elevated concentrations of tryptase may not be detected during the initial 15–30 minutes after the reaction.²⁵ Therefore, samples taken too early may not detect an increase in tryptase concentration. Currently, tryptase concentrations can be used to assess mast-cell involvement but cannot distinguish between anaphylactic and anaphylactoid reactions.^{31,32} In addition, as for histamine, measurement of tryptase concentrations are not widely available in the clinical setting at this time.

Factors to Consider Prior to Desensitization

PENICILLIN ALLERGY

If the patient who develops vancomycin hypersensitivity is receiving vancomycin because of a reported penicillin allergy, steps should be taken to ensure that the allergy is accurate. Approximately 10–20% of hospitalized patients claim a history of penicillin allergy, but studies³³ have shown that many of these patients have been either incorrectly labeled as allergic to penicillin or have lost their sensitivity. Sensitivity to penicillin appears to decrease by approximately 10% per year following an allergic reaction, and it has been observed⁸ that up to 78% of patients with previous reactions to penicillin have a negative skin test after 10 years.

Penicillin skin testing is the single most useful piece of information to aid in assessing an individual's potential for an immediate hypersensitivity reaction to penicillin and should be considered in such patients before vancomycin desensitization.³³

ALTERNATIVE ANTIBIOTICS

Before a vancomycin desensitization procedure is initiated, consideration should be given to the substitution of an alternative antibiotic, if appropriate. Quinupristin/dalfo-

pristin is bactericidal in vitro against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE). Quinupristin/dalfopristin has shown³⁴ effectiveness in the therapy of MRSA, MRSE, and other coagulase-negative staphylococci infections such as bacteremia, nosocomial pneumonia, and skin and soft tissue infection.³⁴ Unfortunately, most of the data supporting its clinical use have come from emergency use trials in small numbers of patients with MRSA or MRSE infections.³⁵ Further studies are required to better categorize the safety and efficacy of quinupristin/dalfopristin in these infections and others, including bone and joint infection, catheter-related bacteremia, and endocarditis.³⁵ Other issues that must be addressed before using this agent include its high incidence of thrombophlebitis, which may necessitate insertion of a central venous line; the need for dosing every eight hours in certain infections, the potential for drug interactions through inhibition of the CYP3A4 system, and an increased drug purchase cost.³⁵

Linezolid is bacteriostatic in vitro against staphylococci, including MRSA and MRSE. It is indicated for the treatment of nosocomial pneumonia and skin and soft tissue infections caused by MRSA. Preliminary results³⁶ examining the efficacy of linezolid against coagulase-negative staphylococcal infections have shown a positive clinical response in 10 of 11 patients. As for quinupristin/dalfopristin, additional studies are needed before routinely using this agent in infections in which it is not indicated. Linezolid does have the unique advantage of step-down oral therapy in patients requiring long-term outpatient therapy. However, adverse reactions such as thrombocytopenia and myelosuppression may prevent or limit its use in certain patients.^{37,38}

Until more experience with these new agents is gained, vancomycin remains the agent of choice in the treatment of β -lactam-resistant gram-positive infections.⁵ However, quinupristin/dalfopristin or linezolid may be alternatives in certain patients with vancomycin hypersensitivity. Consultation with an infectious disease specialist is recommended before substituting one of these agents in a patient who develops vancomycin hypersensitivity. For patients in whom vancomycin is indicated, desensitization is a feasible option and can be performed successfully in the majority of cases.

Vancomycin Desensitization

Vancomycin desensitization is indicated in patients with RMS that does not respond to antihistamine prophylaxis and slowing of the infusion rate. It is also indicated in vancomycin-induced anaphylaxis.

Vancomycin desensitization attenuates mast-cell degranulation by gradually increasing serum vancomycin concentrations over several hours (rapid desensitization) to days (slow desensitization).³⁹ This process eventually renders the mast cells unresponsive to vancomycin. The vancomycin desensitization protocols published in the literature are summarized in Table 1.^{4,11,17,18,20,40,41} Generally, a rapid de-

sensitization protocol should be instituted initially as it will enable therapeutic dosing of vancomycin within 24 hours. This is obviously an advantage as these patients may be acutely ill. Five^{4,17,20,40,41} of the seven published case reports support the use of rapid desensitization. These reports document the successful desensitization of 12 patients using rapid protocols. A rapid protocol has also been used successfully in a hemodialysis patient.⁴ A rapid protocol has also been used successfully in a hemodialysis patient.⁴ The Lerner and Dwyer protocol is outlined in Table 2.⁴¹ Advantages of this protocol are that (1) the entire desensitization procedure can be completed in approximately four hours if the patient is able to tolerate each infusion without requiring repetition of doses, and (2) it only requires the preparation of five dilutions of vancomycin compared with others that require up to 19 different dilutions.²⁰

Slow desensitization should be reserved only for patients who fail a rapid desensitization protocol.¹¹ Unfortunately, it is not known what percentage of patients fail rapid vancomycin desensitization as only successful case reports have been documented, and the incidence of severe hypersensitivity reactions requiring desensitization is low. The slow desensitization protocol described by Lin is outlined in Table 3.¹⁸ This protocol was chosen as it has been used successfully in a patient who failed rapid desensitization¹¹ and, hence, provides a documented alternative should this situation arise.

Clinicians should be aware that mild transient hypersensitivity reactions have been reported in approximately 30% of patients during the course of a drug desensitization procedure.³⁹ Most of the published case reports describe the occurrence of these reactions (Table 1). Mild reactions, such as pruritus, flushing, erythema, and rash may occur during desensitization and do not necessitate discontinuation provided that these symptoms are tolerated by the patient.

Table 2. Rapid Vancomycin Desensitization Protocol (Lerner and Dwyer)⁴¹

Premedication

Diphenhydramine 50 mg iv and hydrocortisone 100 mg iv 15 minutes prior to initiation of protocol, then q6h throughout protocol

Infusion no.	Dilution	Vancomycin Dose (mg)	Concentration (mg/mL)
1	1:10 000	0.02	0.0002
2	1:1000	0.20	0.002
3	1:100	2.0	0.02
4	1:10	20	0.2
5	standard	500	2.0

Preparation

1. Prepare a standard bag of 500 mg vancomycin in 250 mL NS or D5W; label as infusion no. 5, vancomycin 2 mg/mL.
2. Draw up 10 mL of the standard vancomycin 2-mg/mL preparation and place in 100-mL bag of NS or D5W; label as infusion no. 4, vancomycin 0.2 mg/mL.
3. Draw up 10 mL of the 0.2-mg/mL solution and place in a 100-mL bag of NS or D5W; label as infusion no. 3, vancomycin 0.02 mg/mL.
4. Draw up 10 mL of the 0.02 mg/mL solution and place in a 100-mL bag of NS or D5W; label as infusion no. 2, vancomycin 0.002 mg/mL.
5. Draw up 10 mL of the 0.002-mg/mL solution and place in a 100-mL bag of NS or D5W; label as infusion no. 1, vancomycin 0.0002 mg/mL.

Infusion Rate Directions

Initiate infusion rate at 0.5 mL/min (30 mL/h) and increase by 0.5 mL/min (30 mL/h) as tolerated every 5 min to a maximum rate of 5 mL/min (300 mL/h). If pruritus, hypotension, rash, or difficulty breathing occurs, stop infusion and reinfuse the previously tolerated infusion at the highest tolerated rate. This step may be repeated up to three times for any given concentration.

Upon completion of infusion no. 5, immediately administer the required dose of vancomycin in the usual dilution of NS or D5W over 2 h. Decrease rate if pt. becomes symptomatic or, alternatively, increase rate if pt. tolerates dose. Administer diphenhydramine 50 mg po 60 min prior to each dose.

D5W = dextrose 5% in water; NS = NaCl 0.9%.

Table 1. Summary of Published Vancomycin Desensitization Protocols

Reference	Protocol	Premedication	Reaction	Outcome
Lerner and Dwyer (1984) ⁴¹	rapid desensitization (see Table 2)	antihistamine (drug not specified), hydrocortisone 100 mg iv	pruritus, somnolence	1 pt. successfully desensitized twice
Lin (1990) ¹⁸	slow desensitization (see Table 3)	diphenhydramine 50 mg im q6h, ranitidine 150 mg po q12h	mild pruritus	pt. successfully completed 6 wk of full-dose therapy
Anné et al. (1994) ¹¹	rapid (Lerner and Dwyer protocol) then slow (Lin protocol)	diphenhydramine 50 mg im q6h, ranitidine 150 mg po q12h	generalized pruritus and severe burning sensation during rapid protocol; mild pruritus during slow protocol	pt. failed rapid protocol; successfully completed slow protocol and 3-mo full-dose therapy
Wong et al. (1994) ¹⁷	rapid desensitization	various antihistamines (hydroxyzine, astemizole, doxepin, diphenhydramine)	pruritus	successful desensitization in 7 pts.
Villavicencio et al. (1997) ²⁰	rapid desensitization	none, diphenhydramine prn for pruritus	mild pruritus, mild hypotension, oxygen desaturation	pt. successfully completed 5 wk full-dose therapy
Sorensen et al. (1998) ⁴⁰	rapid desensitization	famotidine 20 mg iv q12h	not stated	successful desensitization in peritoneal dialysis patient
Chopra et al. (2000) ⁴	rapid (Lerner and Dwyer protocol)	diphenhydramine 50 mg iv q6h, methylprednisolone 60 mg iv q6h	none	successful desensitization in hemodialysis patient

Table 3. Slow Vancomycin Desensitization Protocol (Lin)¹⁸

Premedication				
Diphenhydramine 50 mg iv 15 minutes prior to protocol initiation, then q6h throughout protocol				
Day	Infusion no.	Dose Provided	Vancomycin Dose (mg)	Concentration (mg/mL)
1	1	0.5 mg in 500 mL	0.5	0.001
2	2	5.0 mg in 500 mL	5.0	0.01
3	3	10 mg in 500 mL	10	0.02
4	4	50 mg in 500 mL	50	0.10
5	4	50 mg in 500 mL	50	0.10
6	5	100 mg in 500 mL	100	0.2
7 ^a	6	100 mg in 250 mL x 2	200	0.4
8	7	150 mg in 250 mL x 2	300	0.6
9	8	250 mg in 250 mL x 2	500	1.0
10	9	500 mg in 250 mL x 2	1000	2.0
11	9	500 mg in 250 mL x 2	1000	2.0
12	9	500 mg in 250 mL x 2	1000	2.0
13	10	1000 mg in 250 mL	1000	4.0
Infusion Directions				
Infuse each dose over 5 h. If pruritus, hypotension, rash, or difficulty breathing occurs, stop the infusion and reinfuse the previously tolerated infusion.				
On day 14, administer the required dose of vancomycin in the usual dilution of NS or D5W (e.g., 1000 mg in 250 mL) at a rate of 100 mL/h. Decrease rate if pt. becomes symptomatic or, alternatively, increase rate if pt. tolerates dose. Consider oral antihistamine prior to each dose.				
D5W = dextrose 5% in water; NS = NaCl 0.9%.				
^a Beginning on day 7, doses are infused consecutively.				

Concomitant administration of medications that induce mast-cell degranulation may also lead to unsuccessful desensitization (Table 4).^{3,7,17,33,42-44} These medications should be temporarily withheld, changed to alternative agents, or given in restricted amounts.⁴⁴ Opioids, in particular, have been well documented to produce a dose-dependent mast-cell degranulation similar to vancomycin; hence, their concurrent administration may produce a synergistic response.^{17,43,44} This synergy may also occur in anaphylactic, IgE-mediated reactions.¹⁷

Table 4. Known Histamine Inducers that May Prevent Successful Desensitization^{3,7,17,33,42-44}

Antibiotics ciprofloxacin, vancomycin	
Barbiturates	
Narcotic analgesics ^a	
Neuromuscular antagonists ^b quaternary amine succinylcholine benzylisoquinolinium compounds atracurium, cisatracurium, doxacurium, mivacurium, tubocurarine	
Propofol	
Plasma expanders dextran, polygeline (Haemaccel)	
Radiocontrast agents	
^a Fentanyl rarely induces histamine release.	
^b Steroidal neuromuscular antagonists cause little or no histamine release (i.e., pancuronium, pipecuronium, rocuronium, vecuronium).	

Desensitization protocols for vancomycin-induced RMS may be initiated on the medical floor if the patient does not have any respiratory or hemodynamic compromise during the initial reaction.¹⁸ A history of respiratory or cardiovascular compromise necessitates the desensitization be conducted in an intensive care unit setting where intravenous access through a central line can be established prior to the protocol initiation. On its successful completion, persistence of the desensitized state depends on the continuous presence of vancomycin.³⁹ Extreme care must be taken to avoid missing even a single vancomycin dose as this may necessitate repeating the entire desensitization procedure.⁴¹ For this reason the desensitization procedure must be repeated each time a separate course of vancomycin is required.

Vancomycin trough concentrations should also be routinely monitored in order to maintain a measurable vancomycin concentration in the blood.⁴ It is not known what minimum concentration is required to maintain the desensitized state but maintenance of vancomycin trough concentrations within the usual therapeutic range should be sufficient.

Summary

Vancomycin desensitization should be considered for severe RMS reactions not responding to premedication and slower rates of infusion, and in anaphylactic reactions to vancomycin when substitution of another antibiotic is not feasible. We have used the rapid protocol first described by Lerner and Dwyer⁴¹ successfully in at least six patients in the past two years who demonstrated both severe anaphylactoid and anaphylactic reactions to vancomycin. Based on the published evidence and our experience, a rapid desensitization protocol should be attempted first as most patients can be successfully desensitized using this method. The rapid desensitization protocols also provide a therapeutic advantage in that they allow normal dosing of vancomycin within 24 hours. Obviously, this is an important practical consideration for patients who are acutely ill and for whom alternative treatments are limited.

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EXTRACTO

OBJETIVO: Discutir la fisiopatología de la reacción de hipersensibilidad inmediata inducida por vancomicina, examinar el proceso de desensibilización a vancomicina, y ofrecer información específica para ordenar y preparar protocolos de desensibilización lenta y rápida.

FUENTES DE INFORMACIÓN: Se hizo una búsqueda de la literatura clínica en el sistema de búsqueda de información MEDLINE de enero de 1966 a febrero de 2001 de artículos en el idioma inglés relacionados con reacciones de hipersensibilidad y desensibilizar a vancomicina. Se utilizaron además fuentes terciarias.

EXTRACCIÓN DE DATOS: Estudios clínicos y reporte de casos publicados en la literatura clínica.

SÍNTESIS: Se discute la fisiopatología de las reacciones de hipersensibilidad inducidas por vancomicina al igual que el procedimiento de desensibilización. El proceso de desensibilización debe considerarse solo en casos en el cual se manifiesta el "síndrome del hombre rojo" (SHR) en el cual el paciente no responde al tratamiento usual y en casos de anafilaxis inducida por vancomicina. La desensibilización rápida es preferida ya que es efectiva en la mayoría de los casos y permite una dosificación terapéutica de vancomicina dentro de las siguientes 24 horas. En los casos en que la desensibilización rápida falla, se puede utilizar el protocolo de desensibilización lenta.

CONCLUSIONES: Las reacciones de hipersensibilidad inducidas por vancomicina incluyen SHR y anafilaxis. La desensibilización a vancomicina debe considerarse para SHR severo que no responde a las medidas usuales y en reacciones anafilácticas a vancomicina cuando la sustitución por otro agente no es viable.

Jorge R Miranda Massari

RÉSUMÉ

OBJECTIF: Discuter des mécanismes impliqués dans les réactions d'hypersensibilité de type immédiat associées à la vancomycine, réviser le procédé de désensibilisation à la vancomycine, et fournir des directives spécifiques pour la prescription et la préparation des protocoles de désensibilisation lente et rapide à la vancomycine.

REVUE DE LITTÉRATURE: Une recherche de la documentation traitant de la désensibilisation et des réactions d'hypersensibilité associées à la vancomycine a été réalisée par MEDLINE (janvier 1966–février 2001). De la documentation tertiaire a aussi été utilisée.

SÉLECTION DE L'INFORMATION: Les présentations de cas et les études cliniques publiées.

RÉSUMÉ: Les mécanismes impliqués dans les réactions d'hypersensibilité associées à la vancomycine sont présentés de même que le procédé de désensibilisation. La désensibilisation devrait être considérée chez les

patients ayant présenté un "red man syndrome" (RMS) qui ne répond pas aux mesures thérapeutiques habituelles et chez les patients ayant présenté une anaphylaxie associée à la vancomycine. Une désensibilisation rapide est préférée puisqu'elle est efficace chez une majorité de patients et qu'elle permet l'utilisation de doses thérapeutiques de vancomycine à l'intérieur de 24 heures. Un protocole de désensibilisation lente peut être tenté chez les patients qui ont eu un échec avec la désensibilisation rapide.

CONCLUSIONS: Les réactions d'hypersensibilité de type immédiat associées à la vancomycine incluent le RMS et l'anaphylaxie. La désensibilisation à la vancomycine devrait être considérée pour les RMS graves qui ne répondent pas aux mesures habituelles et lors de réactions anaphylactiques associées à la vancomycine, quand la substitution par un autre antibiotique n'est pas possible.

Marie Larouche

TABLE I. Characteristics of the subject in relation to the exposure to occupational sensitizers (cyanoacrylate and methacrylate)

	Normal values	At work (3 mo)	Off work (3 wk)	Control inhalation test	Glue inhalation test 30 min exposure	
				7 hr after	7 hr after	24 hr after
Chest symptoms		+++	+	+	++	+
Nose symptoms		+++	0	0	0	0
Treatment		200 µg/day (A) 200 µg/day (B)	200 µg/day (B)	0	0	0
FEV ₁ (L [% pred])	2.2	2.3 (100)	2.5 (108)	2.4 (105)	2.4 (103)	2.6 (114)
VC (L [% pred])	2.7	3.0 (111)	3.0 (111)	3.3 (120)	ND	3.3 (120)
PC ₂₀ (mg/ml)	>16	24	>64	>64	ND	>64
Induced sputum						
TCC (10 ⁶ /ml)	<4.5	1.0	1.3	2.7	3	1.4
Neutrophils (%)	<35	16.2	26.7	28.7	65.5	54.2
Eosinophils (%)	<2	13	0	0	5.8	5
Metachromatic cells (%)	<0.07	0.13	0.06	0	1.5	0.26
Blood eosinophils (10 ⁹ /L)	<0.4	0.5	0.1	0.2	ND	0.4

A, Albuterol; B, budesonide (nasal spray); +++, severe; ++, moderate; +, mild; TCC, total cell count; ND, not done; PC₂₀, provocation concentration of methacholine to cause a fall in FEV₁ of 20%.

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Acute cardiac and pulmonary arrest after infusion of vancomycin with subsequent desensitization

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A 43-year-old woman who had undergone a posterior lumbar fusion with bone grafting and instrumentation 1 week previously was readmitted with a draining-wound hematoma. She subsequently underwent irrigation and debridement after general anesthesia was achieved with-

Abbreviation used

D₅W: 5% dextrose in water

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out complication. After the operation she was doing well with systolic blood pressure readings ranging from 112 to 166 mm Hg. Her postoperative hematocrit level was 31, and serum electrolytes, blood urea, and creatinine values were in the normal range. On postoperative day 2, the patient started receiving vancomycin after intraoperative wound cultures tested positive for methicillin-resistant *Staphylococcus*. One gram of vancomycin in 250 ml of

TABLE I. Desensitization protocol for vancomycin

Dose n ^o .	Dose* (mg)
1	0.005
2	0.010
3	0.020
4	0.040
5	0.080
6	0.160
7	0.320
8	0.640
9	1.25
10	2.50
11	5.00
12	10.00
13	20.00
14	40.00
15	80.00
16	160.00
17	320.00
18	640.00
19	1000.00

*Each dose was given in 50 ml of D₅W infused over 15 minutes by infusion pump except the last dose, which was administered as 25 ml of 1 gm in 250 ml D₅W over 15 minutes. The rest of the solution (1 gm in 250 ml D₅W) was then infused at a rate of 200 ml/hr.

5% dextrose solution was infused at a rate of 250 ml/hour for 1 hour. The patient had no adverse reaction, and the following 12 hours of her postoperative course were unremarkable.

The same dose and rate of vancomycin was then administered for a second time on postoperative day 3. Approximately 2 minutes into the infusion, the patient had acute shortness of breath associated with swelling of the face, lips, and eyelids. She began gasping for air with severe respiratory stridor and subsequently underwent complete respiratory arrest within 3 minutes of the infusion being started. Vancomycin was immediately discontinued, and manual ventilation was attempted by using a bag and face mask with 100% oxygen. This was unsuccessful because of severe upper-airway constriction and presumed bronchospasm. The patient then had severe hypotensive shock and complete cardiovascular collapse, at which point there was no identifiable pulse. Cyanosis developed, and cardiac compressions were begun as she was administered 1 ampule of 1:10,000 epinephrine intravenously along with 2 mg of Narcan.

Large volumes of crystalloid were administered, and there was a significant decrease in resistance to manual ventilation during the next 90 seconds. Cardiac compressions

were stopped when the patient's pulse returned with an initial barely identifiable systolic blood pressure of 40 mm Hg. Although experiencing tachycardia (a heart rate of approximately 150 beats/minute) she was administered a second ampule of 1:10,000 intravenous epinephrine. Because of persistent moderate-to-severe upper-airway obstruction, she required endotracheal intubation and continued manual ventilation. Over the next 10 minutes, her blood pressure rose to 130/70 mm Hg and remained stable thereafter.

Because no other acceptable antibiotic therapy was available, desensitization to vancomycin was performed as outlined in Table I. Throughout the desensitization protocol, the patient had mild itching that responded promptly to intravenous diphenhydramine. Near the end of the desensitization procedure, she had mild hypotension and oxygen desaturation as measured by pulse oximetry after receiving slightly less than the full 250 ml of vancomycin solution (1 gm/250 ml D₅W). These symptoms rapidly reversed with 0.3 ml of 1:1,000 epinephrine administered subcutaneously along with 25 mg of intravenous diphenhydramine). Thereafter, the vancomycin was administered at 1 gm/500 ml D₅W over 2 hours without adverse reaction. She tolerated subsequent doses without difficulty and was discharged with a regimen of 5 weeks of further intravenous vancomycin therapy, which was uneventful.

Vancomycin is being increasingly used because of the growing prevalence of penicillin-resistant organisms.^{1,2} The potentially life-threatening complications associated with the use of vancomycin must be observed, recognized, and treated promptly. This appears to be especially important in patients receiving anesthesia or large doses of narcotics and may be related to the fact that both vancomycin and narcotics induce a dose- or rate-dependent mast-cell degranulation.^{3,4,5}

In patients who have had anaphylactoid reactions to vancomycin, rapid desensitization may be considered when no other suitable antibiotic therapy is available.

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